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Protein Transforms Sperm into Battering Rams

For sperm to penetrate an egg, they must first compress into a tight ball before springing into action. Researchers have now discovered a protein that can affect how DNA is packaged inside sperm so that they can scrunch up tightly enough to pierce the outer layer of the egg during fertilization.

The new studies in mice show that if this key protein is missing, DNA in sperm cannot be tightly packaged and the sperm will not be able to penetrate the egg. The researchers speculate that deficiencies in the protein may underlie some forms of male infertility.

"A small molecule that enhances the enzyme's activity could be a useful fertility drug in cases where compromised function of the gene has caused infertility."

— Yi Zhang

The research team, which was led by Howard Hughes Medical Institute investigator Yi Zhang, published its findings online in *Nature* on October 18, 2007. Zhang and colleagues at the University of North Carolina at Chapel Hill collaborated on the studies with researchers in the Laboratory of Reproductive and Developmental Toxicology at the National Institutes of Health.

In their experiments, Zhang and his colleagues explored the function of the enzyme Jhdm2a, which is a histone demethylase. Histone demethylase enzymes activate genes by snipping molecules called methyl groups from histones. Histone proteins make up the smart stuffing in chromosomes—the core of proteins around which DNA winds so that it is packaged compactly.

Chemical modification of histones — such as the addition or subtraction of methyl groups - is an important mechanism for controlling the activation or repression of genes. This kind of epigenetic control mechanism is separate from other mechanisms that control gene expression, such as regulatory DNA elements that are embedded in the sequences of the genes themselves. Zhang's research group is one of the leaders in establishing the role of

demethylases in regulating gene activity.

The researchers focused on the function of *Jhdm2a* because their earlier studies had indicated that the gene for the protein is highly active in the testis. The protein also interested Zhang and his colleagues because *Jhdm2a* protein levels are highest during sperm maturation.

When the researchers knocked out the *Jhdm2a* gene in mice, they found that the animals' sperm did not mature properly. On closer examination, they found that the genetic material, called chromatin, in the immature sperm of the knockout mice did not condense normally. Sperm chromatin must condense into a compact form in order for fertilization to be successful.

In order for sperm to be able to enter the egg, the sperm chromatin has to be tightly packaged, said Zhang. It must become like a dense ball, so that when it hits the egg, it can penetrate. And in order for this DNA to be tightly packaged, the histone proteins must be replaced by other basic proteins. The basic proteins include transition nuclear protein 1 (*Tnp1*) and protamine 1 (*Prm1*), said Zhang.

The researchers' experiments established that the *Jhdm2a* demethylase specifically activates the *Tnp1* and *Prm1* genes. It does so by binding to the promoter region of the genes, which removes the methyl group that had been keeping the genes silent. Once the methyl group is removed, the *Tnp1* and *Prm1* genes are activated.

Zhang said that although their study was done in mice, it might well have implications for understanding some forms of human infertility. It has been shown that there are many genes in mice that cause infertility when knocked out. But so far few of those genes has been found to be linked to human cases of infertility, he said. However, no one has paid much attention to these demethylase proteins. And since they play such a fundamental role in gene regulation in both mice and humans, there is a possibility that *Jhdm2a* plays a role in some types of human infertility.

Zhang said that drugs that affect the *Jhdm2a* enzyme might have clinical use. A small molecule that enhances the enzyme's activity could be a useful fertility drug in cases where compromised function of the gene has caused infertility, he said. On the other hand, a small molecule that inhibits the enzyme's activity could be a potential birth control drug.